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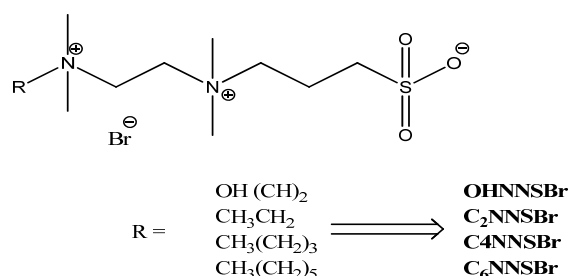
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# Solubility Modifying Power of Zwitterionic Salts

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**Abstract:** Separation of small, hydrophilic molecules from aqueous solutions on one side, and dissolution of hydrophobic organic molecules in water on the other, are nowadays among the most difficult challenges in chemical and bio-technology. Even though these two tasks are seemingly of opposite nature, it is demonstrated herein that both processes can be facilitated by addition of zwitterionic salts, a new class of compounds, which can act either as solubility enhancers or phase separation promoters depending on structure of solute dissolved in an aqueous solution. At a more fundamental level, this study investigates salting in/out propensity of the ions and supports importance of both salt - solute interaction and their concentration.

Addition of salts to an aqueous solution of a solute results in an increase or a decrease of the solute solubility. These phenomena are known as salting in and salting out, respectively.<sup>[1]</sup> The extent of the effects depends on the salt concentration, valence and nature of the cation and the anion, and their complex interactions with water and dissolved solutes.<sup>[2]</sup> Several theories have been used to rationalize underlying mechanisms and predict quantitative and qualitative effects of added salts. The theories have been discussed in great details in several reviews<sup>[1b, 3]</sup> and will be briefly mentioned here. In *hydration theory*<sup>[3d]</sup> the molecules of dissolved solute and salt ions compete for the same water molecules; since the ions have high water affinity and withdrawing power they can dehydrate and precipitate the solute. This approach fails to explain the influence of the structure of dissolved solutes in the salting process and salting in effects. *Water dipole theory*<sup>[3a]</sup> supports the tenet that there is a preferred orientation of water molecules around a polar solute; in the presence of the ions of the same charge water molecules orient favorably and the salting in occurs, while the presence of ions of opposite charge results in a decrease of the solute solubility. A drawback of this theory is that it cannot predict salting effects for different nonpolar solutes. *Electrostatic theory*<sup>[1b, 3a]</sup> suggests that a salt added to aqueous solution influences dielectric constant of the solution; if the dielectric constant of the solution is lower than dielectric constant of water, it leads to salting out phenomenon and *vice versa*. This theory cannot explain different effects found in the solutions of structurally similar salts for the same dissolved solute, and the occurrence of both salting out and salting in effects for different solutes upon addition of the same salt. *Internal pressure theory*<sup>[1b, 3a]</sup> associates salting out and salting in phenomena to negative and positive solution volume changes, respectively, upon addition of salts and supports the behavior of only nonpolar solutes. *Theories based on van der Waals forces*<sup>[3a, 3d]</sup> assume that attractive or repulsive short-range ion-solute interactions are responsible for salting effects. These theories provide a justification of salting in effects found in the solutions of polar and nonpolar solutes upon addition of large ions, as tetraalkylammonium, methylpyridinium, toluenesulfonate, and benzoate ions.<sup>[1b]</sup> This phenomenon is known as hydrotropism.<sup>[4]</sup> Despite huge amounts of experimental<sup>[5]</sup> and molecular simulation<sup>[6]</sup> data published on ion effects in solutions, underlying molecular-level mechanism of their action in solutions has not been well understood.<sup>[2b, 3b, 3d, 7]</sup> Yet, understanding of the effects of ions is crucial to build-up knowledge on functioning and interactions between biological molecules (protein, enzymes, DNA) inside living organisms, but is also of paramount importance for a broad range of applications in chemical and biotechnological fields. The ions behavior is being explored and exploited to control aggregation or crystallization (surfactants, drugs, proteins, polymers)<sup>[8]</sup>, increase stability and solubility in mixtures and formulations (drugs, reactants)<sup>[9]</sup>, or to promote phase separations in bioreactors<sup>[10]</sup>.



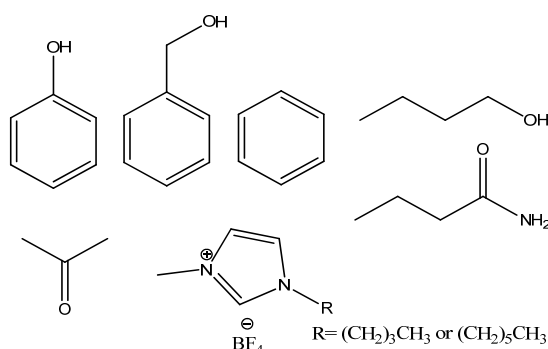
**Scheme 1.** The structures and abbreviations of ZWSs used in the study.

This study investigates effects of addition of zwitterionic salts, (ZWSs) on miscibility and alteration of critical solution temperature (CST) in binary (water (solvent) + organic compound (solute)) systems. ZWSs are novel hybrid materials, incorporating characteristics of inorganic salts, zwitterions, and ionic liquids. Their “ionic liquid” nature gives the opportunity of functionalization of cation and anion leading to i) lower meting points, thus, avoiding problems related to undesirable crystallization, ii) possibility to be used as functional groups attached on long alkyl chains or polymers, and supported on a substrate iii) design consisting of only essential elements based on

ammonium and carboxylate ions and thus improving biodegradability profile and environmental impact. On the other hand, ZWSs like inorganic salts, possess a strong ability to salt in and salt out different dissolved organic molecules. The extent of the salting effects of ZWSs on selected solutes is reported in the manuscript.

Four ZWSs differing in structure and length of the alkyl chain attached, hence, characterized by different hydrophilicity (hydrophobicity), were synthesized according to procedure described previously<sup>[11]</sup> (see ESI). Their structures and abbreviations are given in the Scheme 1.

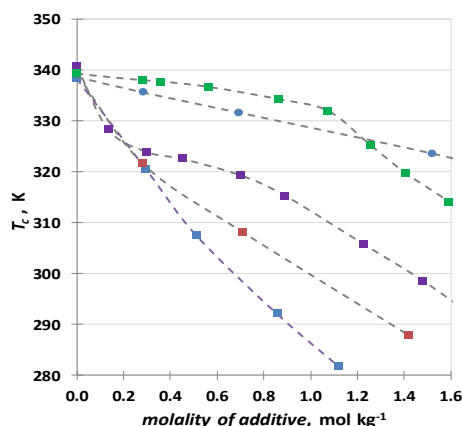
We have selected to explore the effects of added ZWSs on aqueous solubility and CST of several model molecules, listed as follows: i) aromatics: phenol, benzene, and benzyl alcohol, ii) nonaromatic alcohol, butanol, iii) acetone, iv) butyramide, v) two charged molecules, 1-methyl-3-butyl imidazolium tetrafluoroborate ([C<sub>4</sub>mim][BF<sub>4</sub>]) and 1-methyl-3-hexyl imidazolium tetrafluoroborate ([C<sub>6</sub>mim][BF<sub>4</sub>]) (structures given in the Scheme 2). Acetone and butanol were selected for this study because of their industrial relevance; they are products of acetone - butanol - ethanol (ABE) fermentation, which is one of the largest and oldest industrial fermentations.<sup>[12]</sup> However, energy efficient recovery and purification of butanol and acetone from aqueous fermentation broths still present a challenge.<sup>[12-13]</sup> Butyramide was chosen as a model molecule since it structurally corresponds to hydrophilic constituents of peptides and proteins. Phenol is a crystalline material with limited solubility in water, only 8.3 wt% at 20 °C.<sup>[14]</sup> Phenol is used as a starting reactant for synthesis of numerous chemical products: pharmaceuticals, agrochemicals, polymers, epoxides, and detergents. Increasing aqueous solubility of phenol and its derivatives opens possibility of performing chemical processes in aqueous media or design of industrially relevant formulations. A significant number of articles have investigated role and impact of inorganic salts and acid on aqueous solutions of ILs with aim to assess prospect of these systems for industrial extractions and separations. The research covered biphasic systems formed with water - immiscible<sup>[15]</sup>, partially miscible<sup>[16]</sup>, or water - miscible ionic liquids which form aqueous biphasic systems (ABS)<sup>[17]</sup>. Additionally, an understanding of specific ion effects on charged molecules is important from the perspective of a potential to improve solubility and/or bioavailability, or control crystallization of pharmaceuticals which are often in form of salts. ZWSs contain multiple charge centers and possess high hydrophilicity which could lead to specific interactions with solutes; these interactions may have different nature, strength and complexity compared to specific ion effect found in aqueous solutions of common inorganic salts.



**Scheme 2.** The structures of solutes used in the study.

CSTs for the ternary mixtures prepared in this work were determined by cloud point measurements, while NMR and UV absorption spectroscopies were used to determine phase compositions (details of the experimental procedures are provided in the ESI). Typically, the ZWS concentrations in solutions were  $\geq 0.1 \text{ mol kg}^{-1}$  where it is expected that specific ion effects dominate over nonspecific Coulombic interactions.

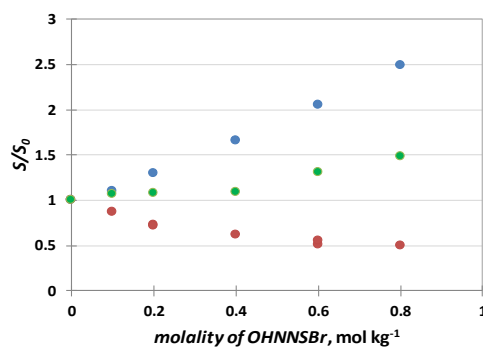
Phenol - water phase diagram has an upper critical solution temperature (UCST) of 339.95 K at the critical composition<sup>[14]</sup>, what makes the study of effect of ZWS addition thorough alteration of CST experimentally convenient. In the Figure 1. the effect of addition of four ZWSs, OHNNSBr, C<sub>2</sub>NNSBr, C<sub>4</sub>NNSBr, and C<sub>6</sub>NNSBr, on CST in system (water + phenol) is presented. The molar ratio of water : phenol was 12.2 : 1 and it has been chosen for providing an easily accessible temperature range. For comparison purposes the effect of addition of a well-known 'water - structure breaker', urea, is also presented in the Figure 1. It has been previously reported that solubility of benzene in aqueous solution follows a reverse sequence of cations of the Hofmeister series.<sup>[1b, 6b, 18]</sup> Hence, a similar behavior could be anticipated in aqueous solutions of benzene and its aromatic derivatives upon addition of ZWSs. Practically, it means that alkyl ammonium cations and sulfonate group<sup>[19]</sup> should act as strong 'chaotropic' or 'water structure breaker' agents, while Br<sup>-</sup> being in the middle of the Hofmeister sequence of anions should only weakly contribute to the overall salting in effect. The results on the effect of addition of four ZWSs on the CSTs of phenol solutions are in good agreement with the proposed statements and all the studied ZWSs herein have displayed salting in effect expressed through suppression of CST. However, the magnitude of the effect is remarkable and higher than the effect measured in the systems with added urea, thiourea<sup>[20]</sup>, or guanidinium chloride<sup>[20]</sup>.



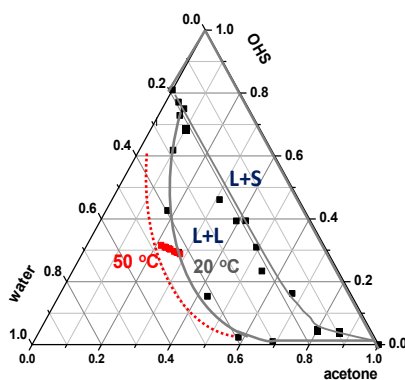
**Figure 1.** The effect of additive concentration, ●urea, ■ C<sub>6</sub>NNSBr, ■ C<sub>4</sub>NNSBr, ■ C<sub>2</sub>NNSBr, ■ OHNNSBr, on CST ( $T_c$ ) in solution (water + phenol) (12.2:1 molar ratio).

It should be also noticed that in the case of C<sub>2</sub>NNSBr and OHNNSBr, CST monotonously decreases with concentration of the additives, while for C<sub>4</sub>NNSBr and, more profoundly, for C<sub>6</sub>NNSBr a complex behavior with a break point in the dependence  $T_c$  versus molality ( $m$ ) was found. This suggests that, probably, two different underlying mechanisms responsible for improved solubility of phenol in water are in place. We assume that short chain C<sub>2</sub>NNSBr and OHNNSBr behave as common inorganic salts in solutions, and origin of increased solubility is electrostatic in nature, achieved by the attraction between two alkyl ammonium cations of the ZWS and  $\pi$ - electrons in phenyl rings. This is supposed to lead to a higher 'local' concentration of ZWS ions in phenol hydration layer comparing to their 'bulk' concentration what is thermodynamically required for salting in process<sup>[21]</sup>. Such interaction prevents  $\pi$  -  $\pi$  stacking that would lead to self-association and phase separation in a solution in absence of ZWSs. Similarly, a recently published molecular simulation study has shown that salting out constants in aqueous solution of benzene upon addition of inorganic salts depend primarily on direct benzene - salt interaction, and not on "solvent effect".<sup>[6b]</sup> NMR study performed in our work (the results and experimental details are presented in ESI) shows that addition of C<sub>2</sub>NNSBr to an aqueous solution of phenol leads to up-field shift of all hydrogen atoms in phenyl ring, indicating that the interaction is not primarily site specific *i.e.* hydrogen-bond, but delocalized over the aromatic ring (Figure 1S). The favorable interaction between phenol and ZWSs provides a higher solubility of phenol and follows well-known Timmermans rule which states that an additive which has high solubility in both phases in a mixture will decrease UCST or increase LCST.<sup>[20, 22]</sup> Indeed, C<sub>2</sub>NNSBr is miscible with neat phenol in a certain concentration and temperature range, what is in contrast with the reported immiscibility in almost all common organic solvents.<sup>[11]</sup> In the case of longer chain C<sub>4</sub>NNSBr and C<sub>6</sub>NNSBr the effect of ZWS addition on CST in system (phenol + water) is, initially, significantly milder. We hypothesize that the reason is bulkiness of the cations that hinders the contact between ZWS - phenol molecules. However, a clear break point in the complex dependence  $T_c$  versus  $m$  can be noticed for C<sub>6</sub>NNSBr, and less clear for C<sub>4</sub>NNSBr (Figure 1.). Once the break point was reached  $T_c$  started to decrease faster as molality of the ZWS increased. The increase of phenol solubility after the break point occurs because of hydrotropic effect. Aggregation behavior of these molecules in aqueous solutions has been studied (see ESI for more details) and it showed that C<sub>6</sub>NNSBr has ability to aggregate, thus forming hydrophobic 'pockets' that can accommodate phenol molecules (see Figure 2S.). The critical aggregate concentration found in the system was 1.1 $m$ , close to the breaking point in the  $T_c$  versus  $m$  dependence (Figure 1.). Interestingly, contrary to the described behavior of ZWSs, it was reported that ability of quaternary alkylammonium bromide salts to salt in benzene was enhanced by increasing the number of methylene groups in the ammonium cation.<sup>[23]</sup> The fact suggests that van der Waals forces probably participate in the process of formation association complexes ZWSs - phenol, but they play only a secondary role.

Furthermore, the study on solubility of benzyl alcohol and benzene in water upon addition OHNNSBr was aimed to assess the contribution coming from hydrogen bonding to overall solubilization process (experimental details given in ESI). The results are presented in Figure 2. and expressed through the ratio  $S/S_0$  versus molality of OHNNSBr, where  $S_0$  is solubility of the solute (benzyl alcohol or benzene) in neat water, and  $S$  the solute solubility in aqueous solution containing OHNNSBr. The solubility of both aromatic molecules increased upon addition of OHNNSBr. The salting in effect is more pronounced for benzyl alcohol, what might be an indication that the hydrogen bonding between hydroxyl group present in the alcohol and the sulfonate group in the ZWS cation also contributes to the molecular attraction. Herein, it is interesting to mention that water solubility of many hydrocarbons (benzene, toluene, butane, propane) is usually reduced by addition of common inorganic salt.<sup>[1b, 21]</sup>



**Figure 2.** Changes in the solubility of benzyl alcohol (●), benzene (●), and butyramide (●) in aqueous solution as a function of OHNNSBr concentration, expressed through a ratio of the solute solubility in OHNNSBr containing aqueous solution (S) and in pure water ( $S_0$ ).



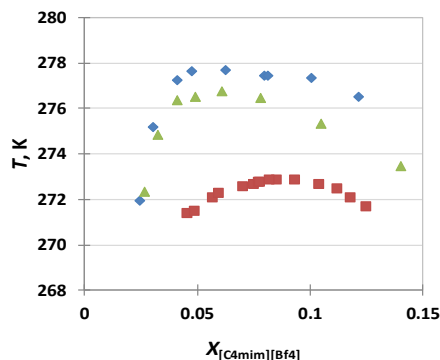
**Figure 3.** Ternary phase diagram of system (water + acetone + OHNNSBr) measured at  $T=293\text{K}$  grey lines, and in the range 293-323K red squares.

The experimental solubility study on aqueous systems of butanol and acetone presented herein, showed that ZWSs can also act as efficient salting out agents. Thus, once more, long-range structuring of water by dissolved ions is ruled out as a governing mechanism in salting in/out phenomena.<sup>[5a, 24]</sup> Binary system (acetone + water) is fully miscible at room temperature. A ternary phase diagram represents the changes this binary system undergoes upon the addition of OHNNSBr (Figure 3.). The phase diagram shows that the OHNNSBr breaks molecular interactions between water and acetone and induces phase splitting into a water - rich and acetone - rich phase. An interesting characteristic of the phase splitting is that a temperature increase promotes the phase separation thus potentially facilitating process of acetone recovery. Even though, the OHNNSBr cannot induce phase separation in a system with low concentration of acetone (see Figure 3.) the obtained results revealed that it can still be used as an entrainer to facilitate separation in gas stripping processes through increased activity coefficient in the mixture.

Furthermore, the effects of ZWSs on phase behavior of binary system (1-butanol + water) were studied. Butanol has a partial solubility in water, with formation of UCST type of phase diagram.<sup>[25]</sup> It was found that the binodal curve in the (1-butanol + water) system is very sensitive to the addition of ZWSs and a temperature shift of 30K was measured after the addition of 0.36 wt% OHNNSBr to the binary system at molar fraction of butanol  $x = 0.48$ . OHNNSBr also promotes phase separation in the region of low butanol concentration (<7 wt%) as presented in Figure 3S. provided in the ESI. Salting out of alcohols was reported also in presence of alkali halides.<sup>[26]</sup> The results showed that despite the possibility of interaction between ZWSs and alcohols via hydrogen-bond formation, or ion-dipole interaction, this association, even if present in a certain extent, does not have a significant positive contribution to mutual miscibility in the studied system. Such behavior of the ZWSs is in a sharp contrast to alkyammonium bromide salts which act as strong salting in agents for alcohols<sup>[27]</sup> because of ion-dipole attraction. The fact stresses importance and complexity of the specific ZWS-solute interactions.

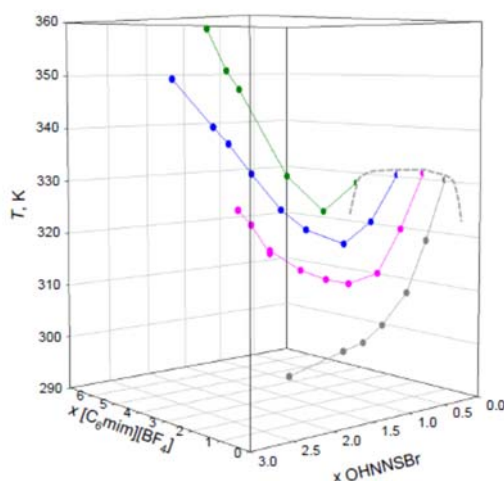
A salting out effect of ZWSs was also found in the system (butyramid + water), as measured by  $^1\text{H-NMR}$  spectroscopy (experimental details given in the ESI) and presented in the Figure 2. Even though butyramid has a

significant dipole moment, and salting in might be expected, the solubility experiments showed a decrease of its solubility in water upon addition of OHNNSBr. This suggests a lack of strong interaction between the molecules. The demonstrated ability of ZWSs to salt out polar peptide group and, expectedly, non-polar group of proteins means that ZWSs represent a group of protein stabilizers rather than denaturants. It is interesting to notice that this behavior is the opposite to the effect of urea which causes protein denaturation.<sup>[28]</sup>



**Figure 4.** Temperature-composition phase diagrams for solutions of  $([C_4mim][BF_4] + H_2O + \text{salt})$  with the salt-to-water molar ratio approx. 0.0025, as a function of the mole fraction of ionic liquid in the solution of  $C_2NNSBr$  (■),  $NaBr$  (▲), and no salt (◆)<sup>24</sup>.

The final part of the study reports on the effect of addition of ZWSs on two charged molecules,  $[C_4mim][BF_4]$  and  $[C_6mim][BF_4]$ . Despite the problems regarding possible hydrolysis at high temperatures reported for these ILs, they have been chosen for this study because of the position of their binodal curves which are located within an experimentally convenient temperature range. An appropriate precaution was given to ensure that the potential decomposition is prevented and reproducibility of measurements achieved. Analysis of the effects of ZWSs on aqueous solutions containing an ionic liquid is significantly more complex compared to the systems consisting of uncharged molecules. In Figure 4, temperature-composition phase diagrams for solutions of  $([C_4mim][BF_4] + H_2O + \text{salt})$  are presented. Contrary to the salting out effect reported for this system in the presence of many inorganic salts, as  $NaCl$ ,  $Na_2SO_4$ , or  $Na_3PO_4$ ,<sup>[16a]</sup> the addition of  $C_2NNSBr$  has an opposite effect and a decrease of CST of 6K was found. A much milder, but still noticeable salting in effect was recorded also in the system with added  $NaBr$ . It leads to conclusion that both the cation and the anion in  $C_2NNSBr$  are responsible for the improved miscibility of the solute.



**Figure 5.** The effect of addition of OHNNSBr on phase behaviour of  $([C_6mim][BF_4] + \text{water})$  system as a function of the salt molality.

In order to elucidate the impact of concentration of ZWS on phase behavior of ILs in water, the experimental approach was extended and designed to correlate concentrations of OHNNSBr and  $[C_6mim][BF_4]$  in water, and

corresponding CSTs, as presented in the diagram given in the Figure 5. A striking contrast in the dependence  $T_c$  versus concentration of OHNNSBr was found for the different molality of  $[C_6mim][BF_4]$ . Namely, for a low concentration of the IL, around 1m, the CST decreases with the concentration of the added ZWS, while for the concentration of the IL higher than 3m, the CST firstly decreases to certain concentrations, and increases afterwards. Obviously, multiple mechanisms of interaction ZWS - IL take place in this concentration range. The reduced miscibility of the IL found in concentrated regime upon addition of the ZWS is explained as follows: the high charge density OHNNS cations form strong hydration complexes with water, and by replacing the water at the solute surface, dehydrate and salt the solute out. The rationale behind the increase of the IL solubility in water at low concentration of the ZWS remains elusive, yet significant in its extent. Although, in some systems (IL + salt (inorganic or ZWS)) there is a possibility of anion exchange that could lead to improved miscibility, in this case, based on the charge density of ion constituents, it is not an expected event. Furthermore,  $^1H$ -NMR and  $^{19}F$ -NMR analyses of phase composition after a complete separation into a water - rich and an IL - rich layers showed no ion-exchange within accuracy provided by NMR spectroscopy. At the current stage and in the absence of additional structural analysis we cannot suggest the molecular-level mechanism responsible for the reported phenomena. The effects of ZWS additives on solubility of a range of organic compounds were analyzed. Contrary to classical inorganic salts that affect solubility of nonpolar or low-polar solutes to very different extents but generally exhibit similar salts order<sup>[1b]</sup>, ZWSs behave differently and do not follow the same salt order. This fact suggests that the displayed salting effects found in the aqueous solutions of ZWSs are related to ZWSs' specific interactions with solutes, rather than to the properties of the electrolyte solutions. It was proposed that ZWSs react with the solutes via non-chemical interactions, such as van der Waals, hydrogen-bond, or  $\pi$ -ion interaction, and these salt - solute interactions dominate effect of water-structuring. The study indicates that in aqueous solutions (ZWS + organics) several mechanisms simultaneously take place giving rise to the effects which cannot be disentangled. The phase diagram of the mixed charge systems (ZWS + IL) shows complex mutual interactions, as reflected by change of shape of demixing loci.

From application point of view, the work provides a tool for prediction of effects of ZWSs on solubility in binary (water + organics) systems and discusses a possible impact on extraction procedures or solubility enhancing technology. The fact that ZWSs have a strong aptitude for salting out analyzed compounds is an indication of a potential to be used as azeotrope breakers or entrainers. They could facilitate removal of ketones and alcohols from aqueous solutions, and reduce energy requirement of gas stripping or pervaporation processes in fermenters or other bioreaction media. Similarly, ZWSs can also promote aggregation, precipitation, and isolation of compounds with amide type structure, e.g. proteins, or bring benefits to design of industrially important formulations. They could also be added as salting out agents to polymer or ionic liquids solutions for extraction, recovery or purification purposes. Additional impact on the proposed applications stemming from the fact that ZWSs offer possibility of modulation and functionalization, good thermal stability, and non-toxicity for the studied microorganisms.<sup>[11]</sup> However, development of suggested potential applications, would require expanding the library of ZWSs with new structures and a systematic study of their interactions with a broad range of molecules.

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